International Journal of TROPICAL DISEASE & Health
4(7): 773-781, 2014

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Prevalence and Laboratory Profile of Hepatitis B Virus Co-infected Nigerian Children with Human Immunodeficiency Virus

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Authors' contributions

This work was carried out in collaboration between all authors. Author EUE designed the study, performed the statistical analysis, wrote the protocol, and wrote the first draft of the manuscript. Authors SO and AOE managed the analyses of the study. Authors ESO, ESY and MOO managed the literature searches. Authors JAA, OOA, JAI, PO and PK reviewed the manuscript. All authors read and approved the final manuscript.

Original Research Article

Received 14th March 2014
Accepted 22nd April 2014
Published 12th May 2014

ABSTRACT

Aims: To determine the prevalence of HBV co-infection in HIV-infected children and compare the baseline laboratory profile of mono-infected and co-infected patients.
Study Design: This was a retrospective cohort study.
Place and Duration of Study: AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Nigeria between January 2008 and December 2012.

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Methodology: We reviewed the clinical records of 452 treatment-naïve children aged 2 months to 15 years confirmed to be HIV positive with Polymerase Chain Reaction (PCR) for children <18 months or Western blot for children ≥18 months. The baseline laboratory tests included: HBsAg, plasma viral load and alanine transaminase (ALT), $CD4^+$T cell count for children ≥5years or $CD4^+$T cell % for children <5years.
Results: Three hundred and ninety-four (87.2%) were mono-infected with HIV while 58 (12.8%) were co-infected with HIV and HBV (HIV/HBV). At baseline, the median viral load was 4.6 log copies/mL for mono-infected compared to 4.7 log copies/mL for HIV/HBV (*P*=.48). The median $CD4^+$T cell count was 366 cells/µL for mono-infected compared to 332 cells/µL for HIV/HBV (*P*=.64). The median $CD4^+$T cell % was 19% for mono-infected compared to 17% for HIV/HBV (*P* =.29). The median ALT level for the whole cohort was 23 IU/L for mono-infected compared to 26 IU/L for HIV/HBV (*P*=.15). However the median ALT level for mono-infected children aged 11-15 years was 28IU/L compared to 43 IU/L for co-infected children of same age (*P* =.008).
Conclusion: A high rate of hepatitis B co-infection was observed in HIV-infected children at our centre; however more severe HIV disease was not observed. Older children co-infected with HBV had significantly higher ALT levels compared to their mono-infected counterparts. Early detection is therefore necessary in order to develop an appropriate treatment plan for children co-infected with HIV and HBV.

Keywords: HIV; hepatitis B; co-infection; CD4+T; viral load; alanine transaminase; Nigeria.

1. INTRODUCTION

Human immunodeficiency virus (HIV) and hepatitis B virus (HBV) are the two most common chronic viral infections seen in the world [1,2]. With an estimated 260,000 children infected with HIV at the end of 2011, Nigeria accounts for more than 10% of the global paediatric HIV burden [3]. Nigeria is also known to be highly endemic for HBV infection [4]. Co-infection with HBV is common among HIV infected children in sub-Saharan African countries. [5-8] the two viruses share common modes of transmission and hence co-exist in the same host at significantly high rates. HBV infections acquired in the perinatal period and early childhood are more likely to lead to chronic infection [9-10]. HIV-infected individuals, particularly those with suppressed immune systems, are less likely to respond to vaccination against HBV and are more likely to develop chronic disease after being exposed to HBV [10]. As more HIV-infected children co-infected with HBV are initiated on highly active anti-retroviral therapy (HAART), they will live longer and complications of chronic HBV infection may become a major health care catastrophe in the coming years especially in resource-limited countries.

The effect of HIV infection on progression of HBV infection in adults is well established [11-12]. Co-infection with HIV modifies the natural history of HBV infection, increasing the rate of viral replication, risk of carriage and chronic hepatitis [11]. HBV infection also increases the toxicity to antiretroviral medications [12]. Co-infection with HBV may lead to rapid progression of HIV disease [7]. Previous studies in adults in Nigeria showed that HIV-infected patients with HBV co-infection had higher HIV ribonucleic acid (RNA) loads and more severe immune suppression prior to initiation of HAART compared to HIV mono-infected patients [13-15].

There is limited information on the effect HBV co-infection has on baseline laboratory profile of HIV-infected children in sub-Saharan African countries. This study therefore aimed to

determine the prevalence and baseline laboratory profile of HIV/HBV co-infected children in Jos, Nigeria.

2. MATERIALS AND METHODS

2.1 Background of Study Area

The study was carried out at AIDS Prevention Initiative in Nigeria (APIN)-supported HIV clinic of Jos University Teaching Hospital, Jos, Plateau State, Nigeria. The programme cares for patients in and outside Plateau state in the North-central zone of Nigeria. HIV care, treatment and support services are free for all patients enrolled in the program.

2.2 Study Design

This was a retrospective cohort study.

2.3 Ethical Consideration

A written informed consent was obtained from parents/guardians for use of data for research. Ethical clearance was obtained from the Ethical committee of Jos University Teaching Hospital.

2.4 Data Collection

The medical records of all treatment-naïve HIV-infected children enrolled in the Paediatric ART program between January 2008 and December 2012 were reviewed for the study. HIV was confirmed by either Amplicor HIV-1 deoxyribonucleic acid Polymerase Chain Reaction (PCR) (Roche Diagnostics, Branchburg, NJ) for children <18 months or Western blot (Immunetics, Cambridge, MA) for children ≥18 months. The baseline laboratory parameters assessed included HBV surface antigen (HBsAg), $CD4^+$T cell count and $CD4^+$T cell percent, viral load, and alanine transaminase (ALT). HBsAg was used to categorize hepatitis status of the patients. HBsAg was determined using enzyme immunoassay (EIA) (Monolisa HBsAg Ultra3; Bio-Rad). HIV RNA levels were measured using Roche COBAS Amplicor HIV-1 monitor test version 1.5 (Roche Diagnostics, GmbH Mannheim, Germany) with a detection limit of 400 copies/ml. Flow cytometry was used to determine $CD4^+$T cell count (Partec, GmbH Munster, Germany) and the $CD4^+$T percent determined by automated method. ALT levels were measured with Roche COBAS C311 Auto Analyser (Roche Diagnostics, GmbH Mannheim, Germany).

2.5 Statistical Analysis

The baseline laboratory parameters of HIV mono-infected patients were compared with those that were co-infected with HBV using nonparametric univariate methods; the Kruskal-Wallis test was used for continuous variables. Linear regression analyses were used to determine whether HBV status was associated with baseline $CD4^+$T cell counts/percent, viral load, or ALT values. *P* value <0.05 was considered significant. Analysis was done with EpiInfo version 3.5.4.

3. RESULTS

Four hundred and fifty-two treatment-naive children aged 2months to 15years were enrolled between January 2008 and December 2012. There were 254 (56.2%) males and 198 (43.8%) females. The mean age for males was 4.24±2.78 years and that of females was 5.34±3.55 years (*P*=.06). Three hundred and ninety-four (87.2%) were mono-infected with HIV while 58 (12.8%) were co-infected with HIV and HBV. The characteristics of the patients are shown in Table 1.

Table 1. Characteristics of the patients

Characteristic	Total (%)
Sex	
Males	254(56.2)
Females	198(43.8)
Age	
<1year	94(20.8)
1-5years	227(50.2)
6-10years	111(24.6)
11-15years	20(4.4)
Hepatitis B status	
Negative	394(87.2)
Positive	58(12.8)

Based on age group, 9.6% of those aged <1 year were co-infected with HBV compared to 11.9% of those aged 1-5 years, 13.5% of those aged 6-10 years and 35% of those aged 11-15 years (*P* =.02) (Table 2). Although more males than females were co-infected with HBV, the differences were not significant (males 13.8%, females 11.6%; *P*=.59).

Table 2. HIV/HBV co-infection based on age groups

Age group	Total (%)	HIV alone	HIV/HBV
<1 year	94(20.8)	85	9
1-5 years	227(50.8)	200	27
6-10 years	111(24.6)	96	15
11-15 years	20(4.4)	13	7
	$X^2 = 9.17$	*P value =.02*	

The median viral load was 4.6 log copies/mL (range, 3.8-6.8 log copies/mL) for mono-infected compared to 4.7 log copies/mL (range, 3.6-6.1 log copies/mL) for HIV/HBV (*P*=.48).

The median $CD4^+$T cell count was 366 cells/µL (range, 4-2322 cells/µL) for mono-infected compared to 332 cells/µL (range, 22-1891 cells/µL) for HIV/HBV (*P*=.64). The median $CD4^+$T cell % was 19% (range, 1-68%) for mono-infected compared to 17% (range, 2-66%) for HIV/HBV (*P*=.29).

The median ALT level was 23 IU/L (range, 2-155 IU/L) for mono-infected compared to 26 IU/L (range, 2-198 IU/L) for HIV/HBV (*P*=.15). Seventy-eight (17.3%) children had elevated ALT (>41IU/L) but there was no difference in the groups: this comprised 63 (16.8%) of children with HIV alone and 15 (19.2%) of co-infected children (*P*=.73).

HBV co-infection was not associated with a reduced $CD4^+$T cell count or $CD4^+$T cell %, or a higher viral load. Co-infection with HBV was however associated with significantly higher median ALT level among children aged 11-15 years (Table 3).

Table 3. Co-infection status and median values of different parameters based on age group

Characteristics	HIV alone (n= 394)	HIV/HBV (n= 58)	*P* value
Median (range) viral load^			
<1year	5.6(4.1-6.8)	5.8(4.5-6.1)	.48
1-5years	4.5(3.8-5.4)	4.4(3.5-5.1)	.86
6-10years	4.7(3.9-6.2)	4.9(3.8-6.0)	.31
11-15years	5.1(4.0-6.5)	5.2(4.2-6.6)	.57
Median (range) $CD4^+$T*			
6-10years	372 (36-1322)	354 (22-1291)	.74
11-15years	237 (4-896)	225 (22-754)	.91
Median (range) $CD4^+$%			
<1years	12 (1-68)	15 (2-66)	.69
1-5years	18 (3-42)	21 (2-54)	.54
Median (range) ALT#			
<1years	26 (2-155)	24 (2-163)	.15
1-5years	21 (8-96)	22 (12-107)	.77
6-10years	23 (2-133)	25 (2-127)	.36
11-15years	28 (4-112)	43 (14-198)	.008

*^ = log copies/mL, * = cells/µL, # = IU/L*

4. DISCUSSION

The prevalence rate of HIV/HBV co-infection in this cohort was 12.8%. The prevalence rate is higher than the rate of 7.7% in children in Benin [5] and 5.8% in Owerri [16] in Nigeria, 1.2% in Tanzania [7], and 4.0% in Kenya. [17] However the rate is lower than HBV prevalence rate of 19.6% reported by Angyo [18] in Jos in 1995 before the inclusion of HBV immunization in the national programme on immunization in 2004, the HIV status was not determined in that study. There is no HBV prevalence data from the general population in children in Jos since implementation of HBV immunization to compare with the present study.

Children in sub-Saharan African countries share similar socio-demographical characteristics that increase the risk of HBV infection. These include transfusion of unscreened blood, injections with contaminated needles and syringes, traditional uvulectomy and scarifications, circumcision and ear piercing with contaminated instruments, frequent skin ulcerations, and sharing of toothbrushes, bath towels and beds. The difference in the prevalence rate of HIV/HBV co-infection in this study and that of other studies may reflect the differences in the geographical distribution, population studies and the methodologies.

A significant number of our patients that were co-infected with HBV were found to be adolescents between the ages of 11–15 years. A similar trend was described in China [19] where children older than 11 years were significantly more infected with HBV. In the US, Toussi [20] found that HIV/HBV co-infected children had a higher median age of 17 years compared to HIV mono-infected children with a median age of 11.4 years. Hepatitis B vaccine was first introduced as part of the National Program on Immunization in Nigeria in

2004, and this may partly explain the reason for a higher HBV co-infection among children within 11–15 years group.

No significant difference was observed in the rate of co-infection with HBV between males and females. This is similar to what was reported in Makurdi, Nigeria. [21]

We did not observe any significant difference in the median viral load, $CD4^+$T cell count and $CD4^+$T cell % between mono and co-infected patients. This is similar to what has been reported in other developing countries. [21-23] In the US, Toussi [20] however reported that HIV/HBV co-infected children had a lower CD4% and a higher HIV RNA levels compared to their mono-infected counterparts.

In this study, 17.3% of the patients had elevated ALT levels. This included 16.8% of mono-infected patients and 18.3% of co-infected patients. Overall, HBV co-infected patients had a slightly higher median ALT level compared to mono-infected patients, but the differences were not significant. This is similar to earlier reports in developing countries and China. [19,21,23] In Tanzania [7] elevated ALT value was shown to be associated with HIV/HBV co-infections in the univariate analysis but not in multivariate analysis. However, a report from USA [20] showed that HBV co-infected children were more likely to have mildly elevated transaminase levels (50%), compared to mono-infected group (19%). Studies have shown that childhood-acquired chronic HBV infection has a long inactive carrier phase; and that acute exacerbation of chronic HBV infection, with reactivation of HBV replication and re-elevation of ALT levels is relatively rare in children, in comparison to adults. [24-27] we however observed that HBV co-infected patients aged 11-15 years had a significantly higher ALT levels compared to mono-infected patients of same age. This may indicate that some of them either had acute HBV infection or reactivation of chronic hepatitis with active viral replication. The HBV co-infected patients with elevated ALT levels were referred to the gastroenterology unit for further evaluation.

The World Health Organization [28] recently recommended including tenofovir (TDF) and emtricitabine (FTC) in initial ARV regimens for children ≥3 years with HBV co-infection as it offers the potential advantage of reducing the selection of HIV resistance to lamivudine (3TC) that may compromise future options for HBV treatment. [29] Presently in Nigeria, TDF is only recommended for adolescents ≥12 years of age. [30] With the availability of TDF in powder form, countries with high prevalence rate of HIV/HBV co-infection like Nigeria should incorporate this recommendation in their guideline on paediatric ART. Harmonizing treatment recommendations with adult regimens could improve children's access to ART. [28] Other benefit of TDF include the ability to combine it with 3TC or FTC and efavirenz (EFV) to create a potent once-daily regimen for children as the lower pill burden will improve adherence [31,32].

Going forward it will be desirable to do a longitudinal study to determine the impact HBV co-infection has on HIV treatment response and hepatotoxicity to anti-retroviral drugs in children.

5. CONCLUSION

A high rate of HBV co-infection was observed in HIV-infected children in this study; however more severe HIV disease was not observed. Older children co-infected with HBV had significantly higher ALT levels compared to their mono-infected counterparts. Early detection

is therefore necessary in order to develop an appropriate treatment plan for children co-infected with HIV and HBV especially as they grow into adolescence.

CONSENT

Not applicable.

ACKNOWLEDGEMENT

This work was supported in part by the US Department of Health and Human Services, Health Resources and Services Administration (U51HA02522) and CDC through APIN (PS 001058). The contents are sorely the responsibility of the authors and do not represent the official views of the funding institutions.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
http://www.sciencedomain.org/review-history.php?iid=503&id=19&aid=4537